Electronic Suppementary Material (ESM)

ESM Table of contents

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ESM Table 1. Characteristics of the on-treatment population. Characteristics of patients in the first imputed dataset. Absolute standardized mean difference (SMD) is shown for each variable as a measure of between-group balance.

	Before PSM			After PSM		
	SGLT2i	**GLP-1RA**	**SMD**	**SGLT2i**	**GLP-1RA**	**SMD**
Number	14282	6153		5643	5643	
Demographics						
Sex male, %	8918 (62.4)	3656 (59.4)	0.06	3457 (61.3)	3395 (60.2)	0.02
Age, years	61.4 (8.9)	61.0 (9.5)	0.04	60.9 (9.1)	60.9 (9.4)	<0.01
Diabetes duration, years	11.8 (8.6)	10.1 (8.0)	0.20	9.8 (7.9)	10.0 (8.0)	0.02
Anthropometrics						
Weight, kg	88.9 (18.1)	94.4 (18.9)	0.30	92.4 (19.1)	93.0 (17.8)	0.03
Height, cm	167.3 (9.7)	167.6 (9.8)	0.02	167.7 (9.9)	167.6 (9.8)	0.01
Body mass index, kg/m2	31.7 (5.9)	33.6 (6.2)	0.31	32.9 (6.2)	33.1 (5.8)	0.04
Waist, cm	109.0 (13.4)	112.9 (13.7)	0.29	111.3 (13.9)	111.9 (12.9)	0.05
Risk factors and laboratory						
Systolic blood pressure, mm Hg	137.6 (18.9)	137.5 (18.8)	<0.01	137.2 (18.7)	137.4 (18.7)	<0.01
Diastolic blood pressure, mm Hg	79.1 (10.1)	80.0 (10.3)	0.09	80.1 (10.2)	80.0 (10.2)	<0.01
Fasting plasma glucose, mg/dl	172.9 (58.3)	163.6 (49.8)	0.17	164.4 (52.0)	164.1 (50.1)	<0.01
HbA1c, mmol/mol %	68.0 (12.1) 8.4 (1.5)	64.0 (10.4) 8.0 (1.3)	0.27	64.0 (11.2) 8.0 (1.4)	64.0 (10.4) 8.0 (1.3)	0.01
Total cholesterol, mmol/l mg/dl	4.5 (1.2) 172.3 (43.8)	4.5 (1.1) 172.8 (43.4)	0.01	4.5 (1.1) 172.5 (42.1)	4.5 (1.1) 172.8 (43.5)	<0.01
HDL cholesterol, mmol/l mg/dl	1.2 (0.4) 46.6 (14.1)	1.2 (0.4) 46.7 (13.5)	<0.01	1.2 (0.4) 46.7 (13.7)	1.2 (0.4) 46.8 (13.5)	<0.01
LDL cholesterol, mmol/l mg/dl	2.5 (1.0) 93.5 (36.5)	2.5 (1.0) 94.7 (36.4)	0.03	2.5 (0.9) 94.5 (35.9)	2.5 (1.0) 94.6 (36.4)	<0.01
Triglycerides, mmol/l mg/dl	1.9 (1.4) 167.7 (128.6)	1.8 (1.3) 162.6 (118.0)	0.04	1.8 (1.2) 162.6 (109.8)	1.8 (1.3) 162.3 (119.9)	<0.01
eGFR (ml/min/1.73 m^2)	86.7 (16.6)	83.9 (20.0)	0.16	86.1 (17.1)	85.7 (18.4)	0.02
Albumin excretion rate, mg/g	66.8 (341.9)	68.1 (328.6)	<0.01	63.2 (364.9)	64.8 (310.0)	<0.01
eGFR slope (ml/min/1.73 m^2/year)	-0.3 (17.5)	-0.6 (19.3)	0.02	-0.6 (21.8)	-0.4 (19.7)	<0.01
Complications						
Chronic kidney disease, %	878 (6.1)	815 (13.2)	0.26	472 (8.4)	502 (8.9)	0.02
Pathologic albuminuria, %	2332 (16.3)	1008 (16.4)	<0.01	875 (15.5)	902 (16.0)	0.01
Diabetic Retinopathy; %	2708 (19.0)	812 (13.2)	0.15	704 (12.5)	717 (12.7)	<0.01
Diabetic macular edema, %	386 (2.7)	104 (1.7)	0.07	89 (1.6)	93 (1.6)	<0.01
Stroke / TIA; %	214 (1.5)	83 (1.3)	0.01	57 (1.0)	72 (1.3)	0.03
Carotid atherosclerosis, %	2848 (19.9)	1198 (19.5)	0.01	990 (17.5)	1085 (19.2)	0.04
Ischemic heart disease; %	2088 (14.6)	642 (10.4)	0.12	619 (11.0)	604 (10.7)	<0.01
Left ventricular hypertrophy, %	1103 (7.7)	437 (7.1)	0.02	400 (7.1)	391 (6.9)	<0.01
Heart failure, %	478 (3.3)	142 (2.3)	0.06	155 (2.7)	132 (2.3)	0.03
Any site revascolarization, %	1476 (10.3)	484 (7.9)	0.08	461 (8.2)	448 (7.9)	<0.01
Microvascular complications, %	5450 (38.2)	2260 (36.7)	0.03	1868 (33.1)	1899 (33.7)	0.01
Macrovascular complications, %	5097 (35.7)	1911 (31.1)	0.10	1745 (30.9)	1746 (30.9)	<0.01
Established CVD, %	2491 (17.4)	803 (13.1)	0.12	747 (13.2)	747 (13.2)	<0.01
Glucose lowering medications						
Metformin, %	11366 (79.6)	5049 (82.1)	0.06	4719 (83.6)	4719 (83.6)	<0.01
Sulphonylurea / repaglinide, %	883 (6.2)	759 (12.3)	0.23	603 (10.7)	641 (11.4)	0.02

Pioglitazone, %	231 (1.6)	287 (4.7)	0.19	179 (3.2)	206 (3.7)	0.03
Acarbose, %	87 (0.6)	29 (0.5)	0.02	29 (0.5)	27 (0.5)	<0.01
Bolus insulin, %	4206 (29.4)	188 (3.1)	0.67	189 (3.3)	188 (3.3)	<0.01
Basal insulin, %	6231 (43.6)	1462 (23.8)	0.42	1294 (22.9)	1307 (23.2)	<0.01
Other medications						
Statins, %	8203 (57.4)	3312 (53.8)	0.07	3014 (53.4)	3035 (53.8)	<0.01
Anti-platelet agents, %	5831 (40.8)	2218 (36.0)	0.10	1996 (35.4)	2002 (35.5)	<0.01
RAS blockers, %	8478 (59.4)	3650 (59.3)	<0.01	3302 (58.5)	3318 (58.8)	<0.01
Beta blockers, %	4325 (30.3)	1765 (28.7)	0.03	1617 (28.7)	1593 (28.2)	<0.01
Calcium channel inhibitors, %	3048 (21.3)	1398 (22.7)	0.03	1249 (22.1)	1245 (22.1)	<0.01
Diuretics, %	4140 (29.0)	2035 (33.1)	0.09	1735 (30.7)	1789 (31.7)	0.02
Anticoagulants, %	349 (2.4)	153 (2.5)	<0.01	144 (2.6)	125 (2.2)	0.02

Abbreviations: eGFR, estimated glomerular filtration rate according to the CKD-EPI equation. CKD, chronic kidney disease. TIA, transient ischemic attack. CVD cardiovascular disease. RAS, renin angiotensin system.

ESM Table 2. Study endpoints in the various populations.

	Entire population		Without baseline CKD	
	ITT	**OT**	**ITT**	**OT**
N/group	5701	5624	4416	4354
Primary outcome				
Change in eGFR, ml/min/1.73 m^2	1.19 (0.47; 1.90)	1.45 (0.72; 2.19)	1.12 (0.43; 1.81)	1.12 (0.42; 1.82)
Secondary outcomes				
Difference in total eGFR slope, ml/min/1.73 m^2/year	0.53 (0.30; 0.76)	0.54 (0.28; 0.80)	0.52 (0.26; 0.77)	0.58 (0.29; 0.87)
Difference in chronic eGFR slope, ml/min/1.73 m^2/year	0.55 (0.28; 0.81)	0.67 (0.34; 1.00)	0.48 (0.17; 0.79)	0.67 (0.30; 1.03)
Change in UACR, mg/g	-22.18 (-52.34; 7.98)	-19.29 (-47.92; 9.35)	2.97 (-1.14; 7.07)	2.47 (-1.58; 6.52)
New-onset CKD, HR (95% C.I.)	0.86 (0.73; 1.01)	0.83 (0.69; 0.99)	0.84 (0.69; 1.03)	0.83 (0.66; 1.05)
Worsening CKD class, HR (95% C.I.)	0.92 (0.86; 0.99)	0.93 (0.86; 0.99)	0.89 (0.82; 0.96)	0.90 (0.83; 0.98)
Sustained ≥40% eGFR reduction, HR (95% C.I.)	0.78 (0.60; 1.02)	0.83 (0.62; 1.11)	0.79 (0.57; 1.10)	0.83 (0.59; 1.17)
Sustained ≥57% eGFR reduction, HR (95% C.I.)	0.64 (0.41; 0.99)	0.65 (0.39; 1.09)	0.64 (0.35; 1.19)	0.71 (0.39; 1.27)
New-onset macroalbuminuria, HR (95% C.I.)	1.15 (0.87; 1.51)	1.05 (0.76; 1.46)	2.03 (1.14; 3.63)	1.80 (0.93; 3.50)
Intermediate endpoints				
Change in HbA^{1c}, mmol/mol	1.8 (1.5; 2.1)	1.8 (1.5; 2.2)	1.8 (1.4; 2.1)	1.8 (1.5; 2.2)
%	0.23 (0.19; 0.26)	0.23 (0.19; 0.27)	0.22 (0.18; 0.26)	0.23 (0.19; 0.28)
Change in body weight, kg	-1.26 (-1.98; -0.54)	-1.26 (-1.98; -0.54)	-1.35 (-2.16; -0.54)	-1.50 (-2.31; -0.68)
Change in systolic blood pressure, mm Hg	-1.11 (-1.76; -0.45)	-1.21 (-1.92; -0.50)	-0.95 (-1.68; -0.22)	-0.97 (-1.75; -0.20)
Change in diastolic blood pressure, mm Hg	-0.62 (-0.98; -0.27)	-0.64 (-1.02; -0.27)	-0.56 (-0.95; -0.16)	-0.60 (-1.01; -0.18)

Abbreviations: ITT, intention-to-treat. OT, on-treatment. CKD, chronic kidney disease. UACR, urinary albumin excretion rate. HR, hazard ratio
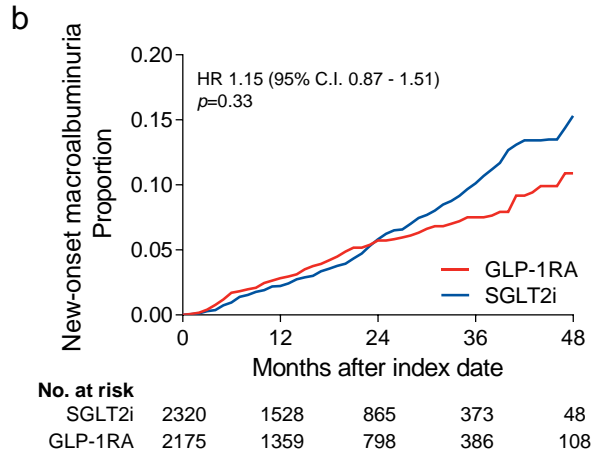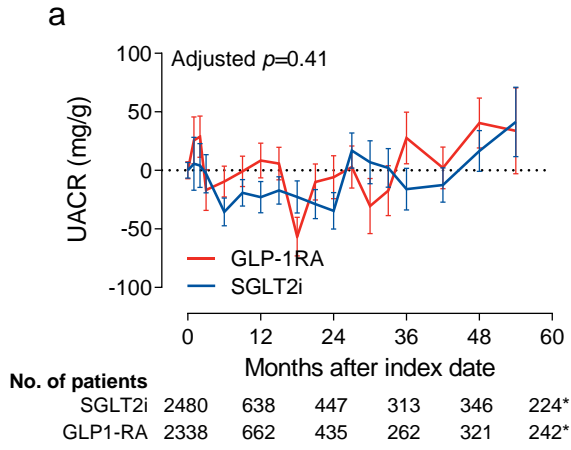
ESM Table 3. Characteristics of the population without baseline CKD. Characteristics of patients in the first imputed dataset. Absolute standardized mean difference (SMD) is shown for each variable as a measure of between-group balance.

	Before PSM			After PSM		
	SGLT2i	GLP-1RA	SMD	SGLT2i	GLP-1RA	SMD
Number	11421	4594		4430	4430	
Demographics						
Sex male, %	6981 (61.1)	2647 (57.6)	0.07	2605 (58.8)	2572 (58.1)	0.02
Age, years	61.0 (8.9)	59.9 (9.5)	0.11	60.2 (9.1)	60.0 (9.5)	0.02
Diabetes duration, years	11.4 (8.5)	9.4 (7.7)	0.24	9.4 (7.6)	9.4 (7.7)	<0.01
Anthropometrics						
Weight, kg	88.1 (18.0)	93.8 (18.9)	0.32	92.2 (18.9)	92.9 (18.0)	0.04
Height, cm	167.2 (9.8)	167.5 (9.9)	0.03	167.5 (9.8)	167.5 (9.9)	<0.01
Body mass index, kg/m2	31.5 (5.8)	33.4 (6.2)	0.34	32.8 (6.2)	33.1 (5.8)	0.05
Waist, cm	108.4 (13.2)	112.3 (13.6)	0.29	110.9 (14.1)	111.4 (12.8)	0.04
Risk factors and laboratory						
Systolic blood pressure, mm Hg	137.2 (18.7)	136.7 (17.9)	0.03	136.4 (18.6)	136.5 (17.8)	<0.01
Diastolic blood pressure, mm Hg	79.1 (10.0)	80.1 (10.0)	0.09	80.1 (10.1)	80.0 (10.0)	<0.01
Fasting plasma glucose, mg/dl	171.5 (58.0)	162.2 (49.4)	0.17	162.3 (50.5)	162.4 (49.6)	<0.01
HbA1c, mmol/mol %	67.0 (12.1) 8.3 (1.5)	64.0 (9.6) 8.0 (1.2)	0.26	64.0 (10.4) 8.0 (1.3)	64.0 (9.6) 8.0 (1.2)	<0.01
Total cholesterol, mmol/l mg/dl	4.6 (1.1) 173.1 (43.6)	4.6 (1.2) 173.7 (43.9)	0.01	4.6 (1.1) 173.4 (42.4)	4.6 (1.2) 173.8 (43.9)	<0.01
HDL cholesterol, mmol/l mg/dl	1.2 (0.4) 47.1 (14.1)	1.2 (0.4) 47.3 (14.1)	0.01	1.2 (0.4) 47.4 (13.7)	1.2 (0.4) 47.3 (14.1)	<0.01
LDL cholesterol, mg/dl	2.5 (1.0) 94.7 (36.9)	2.5 (1.0) 96.3 (36.7)	0.04	2.5 (0.9) 95.4 (36.0)	2.5 (1.0) 96.3 (36.7)	0.02
Triglycerides, mmol/l mg/dl	1.8 (1.4) 162.8 (126.2)	1.8 (1.4) 156.7 (124.9)	0.05	1.8 (1.2) 158.0 (108.9)	1.8 (1.4) 157.1 (126.4)	<0.01
eGFR (ml/min/1.73 m^2)	89.1 (14.0)	89.9 (14.3)	0.06	89.7 (14.1)	89.9 (14.3)	0.01
Albumin excretion rate, mg/g	10.4 (7.4)	10.3 (7.3)	<0.01	10.2 (7.3)	10.3 (7.3)	0.01
eGFR slope (ml/min/1.73 m^2/year)	-0.5 (25.8)	0.0 (24.0)	0.02	0.3 (16.3)	-0.1 (23.9)	0.02
Complications						
Chronic kidney disease, %	0 (0.0)	0 (0.0)	0.02	0 (0.0)	0 (0.0)	<0.01
Pathologic albuminuria, %	0 (0.0)	0 (0.0)	<0.01	0 (0.0)	0 (0.0)	<0.01
Diabetic Retinopathy; %	1920 (16.8)	475 (10.3)	0.18	472 (10.7)	460 (10.4)	<0.01
Diabetic macular edema, %	258 (2.3)	58 (1.3)	0.07	61 (1.4)	57 (1.3)	<0.01
Stroke / TIA; %	161 (1.4)	48 (1.0)	0.03	51 (1.2)	46 (1.0)	0.01
Carotid atherosclerosis, %	2102 (18.4)	794 (17.3)	0.03	724 (16.3)	771 (17.4)	0.03
Ischemic heart disease; %	1559 (13.7)	404 (8.8)	0.15	424 (9.6)	402 (9.1)	0.02
Left ventricular hypertrophy, %	794 (7.0)	281 (6.1)	0.03	272 (6.1)	269 (6.1)	<0.01
Heart failure, %	346 (3.0)	80 (1.7)	0.08	101 (2.3)	80 (1.8)	0.03
Any site revascolarization, %	1116 (9.8)	308 (6.7)	0.11	324 (7.3)	308 (7.0)	0.01
Microvascular complications, %	2504 (21.9)	647 (14.1)	0.20	646 (14.6)	627 (14.2)	0.01
Macrovascular complications, %	3812 (33.4)	1276 (27.8)	0.12	1264 (28.5)	1244 (28.1)	0.01
Established CVD, %	1863 (16.3)	507 (11.0)	0.15	530 (12.0)	503 (11.4)	0.02
Glucose lowering medications						
Metformin, %	9227 (80.8)	3896 (84.8)	0.10	3796 (85.7)	3771 (85.1)	0.02
Sulphonylurea / repaglinide, %	731 (6.4)	553 (12.0)	0.21	480 (10.8)	507 (11.4)	0.02

Pioglitazone, %	195 (1.7)	237 (5.2)	0.21	149 (3.4)	180 (4.1)	0.04
Acarbose, %	69 (0.6)	22 (0.5)	0.02	23 (0.5)	22 (0.5)	<0.01
Bolus insulin, %	3095 (27.1)	98 (2.1)	0.65	98 (2.2)	98 (2.2)	<0.01
Basal insulin, %	4728 (41.4)	944 (20.5)	0.44	930 (21.0)	921 (20.8)	<0.01
Other medications						
Statins, %	6353 (55.6)	2308 (50.2)	0.11	2244 (50.7)	2248 (50.7)	<0.01
Anti-platelet agents, %	4402 (38.5)	1485 (32.3)	0.13	1465 (33.1)	1450 (32.7)	<0.01
RAS blockers, %	6381 (55.9)	2537 (55.2)	0.01	2433 (54.9)	2444 (55.2)	<0.01
Beta blockers, %	3281 (28.7)	1182 (25.7)	0.07	1174 (26.5)	1158 (26.1)	<0.01
Calcium channel inhibitors, %	2199 (19.3)	916 (19.9)	0.02	905 (20.4)	877 (19.8)	0.02
Diuretics, %	3058 (26.8)	1369 (29.8)	0.07	1273 (28.7)	1299 (29.3)	0.01
Anticoagulants, %	247 (2.2)	84 (1.8)	0.02	87 (2.0)	81 (1.8)	<0.01

Abbreviations: eGFR, estimated glomerular filtration rate according to the CKD-EPI equation. CKD, chronic kidney disease. TIA, transient ischemic attack. CVD cardiovascular disease. RAS, renin angiotensin system.

ESM Figure 1. Change in albuminuria in the primary ITT analysis. a) Change from baseline in albuminuria on the continuous scale. Numbers below indicate patients who contributed with values at each time point. b) Kaplan-Meier curves for new-onset macroalbuminuria in the two groups. Numbers below indicate patients at risk. *observation closed at 54 months.

a)

Adjusted *p*=0.41

No. of patients					
SGLT2i	2480	638	447	313	346	224*
GLP1-RA	2338	662	435	262	321	242*

b)

HR 1.15 (95% C.I. 0.87 - 1.51)
p=0.33

No. at risk					
SGLT2i	2320	1528	865	373	48
GLP-1RA	2175	1359	798	386	108

ESM Figure 2. Categorical outcomes in the OT population. The forest plot illustrates the most important outcomes in the on-treatment (OT) population. Tabular results are presented as crude rates in each group, hazard ratios (HR) and 95% confidence intervals (C.I.) along with their p-values.

Endpoint	Crude rates / 1000 PYE		Adjusted hazard ratio (95% C.I.)	p-value
	SGLT2i	GLP.1RA		
New-onset CKD	25.7	31.3	0.83 (0.69 - 0.99)	0.041
Worsening CKD class	240.2	260.7	0.93 (0.86 - 0.99)	0.037
Sustained >40% eGFR reduction	15.0	18.2	0.83 (0.62 - 1.11)	0.217
Sustained >57% eGFR reduction	4.4	6.7	0.65 (0.39 - 1.09)	0.110
New-onset macroalbuminuria	23.8	23.0	1.05 (0.76 - 1.45)	0.749
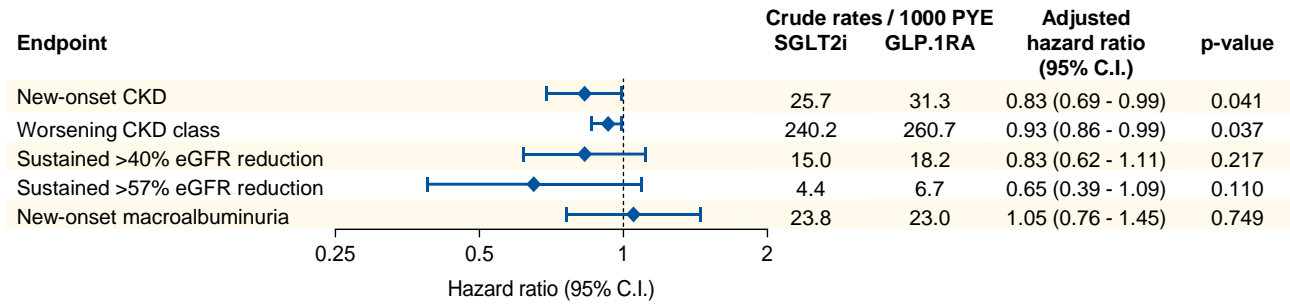
ESM Figure 3. Main results in the population without baseline CKD. a) Change in eGFR (primary outcome) in the two groups. b) Kaplan-Meier curve for the worsening of CKD class. c) Change in albuminuria in the two groups. d) Kaplan-Meier curve for new-onset macroalbuminuria. In a) and c), the table below shows the number of patients contributing with values to the model. In b) and d), the table below shows the number of patients at risk. e) Forest plot of kidney outcomes. Tabular results are presented as crude rates in each group, hazard ratios (HR) and 95% confidence intervals (C.I.) along with their p-values.